

Structure of the mitochondrial cytochrome bc₁ complex at 2.1 Å.

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Mitochondria serve as the power supplies of the cell. The respiratory chain oxidizes organic substrates and stores part of the energy released as a transmembrane gradient in electrochemical potential of the hydrogen ion. This gradient is in turn utilized to power ATP synthesis, transport, or other energy-requiring processes. A major component of the respiratory chain is the cytochrome bc₁ complex, or ubiquinol:cytochrome c oxidoreductase. It is a membrane-embedded complex of 11 protein chains with three hemes and an Fe₂S₂ cluster, which oxidizes ubiquinol and reduces cytochrome c, coupling the energy released to translocation of protons across the membrane. In the last decade several groups crystallized this membrane protein complex and solved the structure at around 3 Å. These low resolution structures provided the general folding and packing of the complex, and led to the realization that the extrinsic domain of the iron-sulfur protein is mobile. However the resolution limited the interpretability of details like substrate and inhibitor binding and proton pathways.

In 2001 we developed a new orthorhombic crystal form of the bovine cytochrome bc₁ complex, and in 2002 during work at the ALS and SSRL we have made dramatic improvements in resolution with this crystal form. The improvement has come mainly from a new purification step involving fractional precipitation with PEG, and from optimization of crystal freezing and dehydration techniques. While this optimization is still going on, we already have crystals diffracting beyond 2 Å and we are refining the structure against 2.0 Å data with an R-factor below 0.4 in the shell at 2.1 Å. We anticipate that this crystal form will be excellent for studying the binding of substrates, products, and inhibitors at the quinol reductase site. While model building and refinement is still proceeding, the electron density is already excellent in most parts of the structure. The Figure shows electron density around the pharmacophore of the inhibitor Antimycin A in its binding site. (Funded by NIH award R01DK44842 to E.A.Berry)



Figure 1. Electron density map (2.1 Å 2Fo-Fc, B= -20, contoured at 1.8 σ) around the salicylate ring of antimycin in the new orthorhombic crystal of bovine cytochrome bc₁.

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